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Cognitive therapy for patients with schizophrenia - authors' reply

Citation for published version:

Morrison, AP, Dunn, G, Turkington, D, Pyle, M & Hutton, P 2014, 'Cognitive therapy for patients with schizophrenia - authors' reply', *The Lancet*, vol. 384, no. 9941, pp. 401-402. [https://doi.org/10.1016/S0140-6736\(14\)61275-7](https://doi.org/10.1016/S0140-6736(14)61275-7)

Digital Object Identifier (DOI):

[10.1016/S0140-6736\(14\)61275-7](https://doi.org/10.1016/S0140-6736(14)61275-7)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

The Lancet

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We thank our correspondents for giving us the opportunity to respond to their methodological and statistical queries and provide additional information on the process and outcome of our trial. Our trial was not designed to change clinical practice. It was a preliminary trial, which needs to be followed up by a larger, pragmatic multicentre study, as we stated in both the abstract and the full article. It is important not to over-interpret our data, and we explicitly advised against discontinuation of medication. We claimed the trial demonstrated that CT was “safe and acceptable”, not “safe and effective”. There were no participants included on the basis of attenuated psychotic symptoms (our entry criteria included positive symptoms above a threshold on the PANSS). Our combined sample had a mean baseline PANSS score of 72, with the recommended cut-offs for mildly ill being 58 and moderately ill being 75; therefore, our sample consists of people with both levels of difficulty. Duration of psychosis and other sample characteristics are reported elsewhere (1). We can clarify that the proportion starting medication in each arm was 27%. An investigation of the fidelity/components of therapy is being undertaken and will be published. Standardised effect sizes (and 95% CIs) for the PANSS subscales are as follows: PANSS positive (-0.45, -0.81 to -0.09), PANSS negative (-0.22, -0.51 to +0.07), PANSS general (-0.47, -0.78 to -0.16). The claim that missing data is over 50% at follow-up points is based on using the randomised N as denominator, rather than the number who could have potentially provided outcome assessments given the planned variable length of follow-up (adopted to provide value for money to the funder, allowing maximal recruitment and the most complete data we could gather in the lifetime of the trial). The proportion of non-missing PANSS data at 9 months (the final point at which an outcome assessment could have been provided by all randomised participants) is about 61%, and at 18 months (using those who could have been followed up within that timeframe as the denominator) is about 67% (see Table 2 of Morrison *et al.*), which are far from ideal, but would be considered acceptable.

Two of the letters appear to question the use of a mixed (random) effects model based on an assumption that outcome data are “Missing at Random” (MAR). We tried to avoid technical jargon concerning the statistical modelling, but we did provide a technical reference to indicate what was meant by MAR (2). Its meaning is not quite the same as implied in everyday English, the latter having the technical description more akin to “Missing Completely at Random” (MCAR). Clearly, MCAR does not hold. The MAR assumption will only ever be an approximation to the truth (like the modelling assumptions behind any statistical analyses). Our critics seem to assume that if the “correct” missing data mechanism had been chosen then the estimated treatment effect would be closer to the null. We suggest they would not have been prepared to accept modifications to the pre-specified analysis if it led to a greater treatment effect. As we drift away from the pre-specified statistical analysis plans the risk of selecting methods of analysis that favour the outcomes we are looking for becomes a much more serious cause of concern than minor departures for the assumptions underlying the main analyses. Although missing data lead to lower precision (lower statistical power) as well as potential biases, the fact that in the present trial we found statistically significant effects implies that in the event it was not underpowered. Lack of power would only have been a serious concern if we’d observed an apparently promising but statistically insignificant result.

Responding to the hypothesis concerning loss to follow-up in generic community services (CS) versus early intervention services (EIS), we had 9-month PANSS outcomes for 10/20 (50%) and 12/17 (71%) of those allocated to CT in EIS and CS, respectively. The corresponding numbers for TAU were 15/22 (68%) and 8/15 (53%). Comparing the proportions of missing data in the four groups, chi-square =

2.52 (df=3, p=0.472). We check the sensitivity of our results to this by adding service type as an extra covariate in the mixed-effects model (again assuming MAR). The revised estimate of the treatment effect on PANSS total is -6.64 (s.e. 2.17), the original estimate being -6.52 (s.e. 2.18). Adding a treatment by service interaction to the mixed model, the effect of CT in EIS participants is estimated to be -10.97 (s.e. 2.78; p<0.001) and the interaction is estimated to be +9.92 (s.e. 4.22; p=0.019), implying that there is little or no CT effect in CS participants (i.e. -10.97+9.92=-1.05). See Table 1 for means for each group. We note that this finding (if real) may not have arisen through differences in the type of service *per se*, but could be explained by age differences (see Table 1).

Analysis of the confounding effects of medication would be overly complex for a pilot trial, given the varying time points at which it commenced and, more importantly, changes in medication are themselves an outcome of the treatment (i.e. potential mediators rather than confounders); we report the data and it would appear there is no clear pattern. We recognise that it may have had an effect, but with equal proportions in both arms it cannot account for the between group differences observed.

Table 1

	CT PANSS Total At 9 months Mean (SD)	TAU PANSS Total At 9 months Mean (SD)	Age Mean (SD)
Early Intervention Services	54.20 (12.35)	63.73 (15.69)	23.45 (6.43)
Other Community Services	61.08 (16.75)	62.38 (7.39)	41.63 (11.12)